(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 671 389 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **95103196.2**

(22) Date of filing: **06.03.95**

(51) Int. Cl.[6]: **C07D 207/08**, C07D 401/06, C07D 401/12, C07D 405/12, C07D 403/06, C07D 401/14, C07D 403/12, C07D 471/04, C07D 409/12, A61K 31/40

(30) Priority: **08.03.94 JP 37187/94**

(43) Date of publication of application:
13.09.95 Bulletin 95/37

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

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(54) 3-Phenylpyrrolidine derivatives.

(57) 3-phenylpyrrolidine derivatives of the present invention effectively inhibit phosphodiesterase (PDE) IV activities so that they can be used as medicaments for, such as, the asthma.

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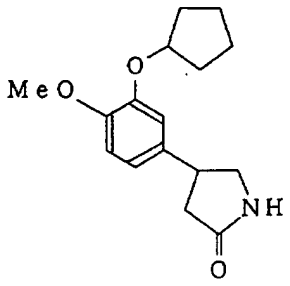
FIELD OF THE INVENTION

The present invention relates to new 3-phenylpyrrolidine derivatives, and more specifically, to 3-phenylpyrrolidine derivatives ensuring inhibition of phosphodiesterase (PDE) IV activities, their optical isomers, salts, N-oxide derivatives, hydrates or solvates.

BACKGROUND OF THE INVENTION

cAMP (cyclic adenosine 3', 5'-monophosphate) is an important second messenger which participates in relaxing bronchial smooth muscles and regulating functions of inflammatory cells. cAMP is decomposed into inactive 5'-AMP by phosphodiesterase (PDE). Accordingly, if the decompostion by PDE is suppressed to increase intracellular concentrations of cAMP, it is considered that bronchial dilatation and anti-inflammatory effects can be obtained so that concerns have been running high for PDE inhibitors (suppressing decomposition of cAMP) as antiasthmatics. Further, recently, five kinds of PDE isozymes (PDE I, II, III, IV, V) have been identified and their tissue distributions have been revealed(Adv. Second Messenger Phosphoprotein Res., 22, 1 (1988), Trends Pharm., Sci., 11, 150 (1990)).

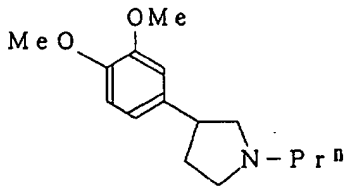
Among the inhibitors against these isozymes, possibility has been pointed out that the specific inhibitors of PDE IV are effective in treating asthma (Thorax, 46, 512 (1991)). As a compound having the specific inhibition of PDE IV, for example, a compound (rolipram xxx) disclosed in Japanese First (unexamined) Patent Publication No. 50-157360 is known as represented by the following formula:



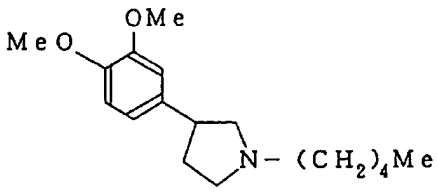
(roliplam)

Although various compounds are known other than the foregoing as disclosed in, such as, Japanese First (unexamined) Patent Publications No. 4-253945 and 5-117239, WO9115451, WO9207567, EP497564, WO9219594, they have not applied clinically up to date so that development of further useful compounds has been demanded.

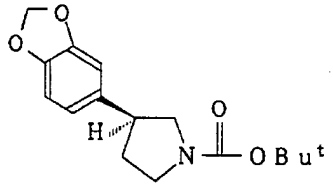
In J. Pharm. Sci., 73, 1585 (1984), a compound represented by the following formula and its dopaminergic activity are described:



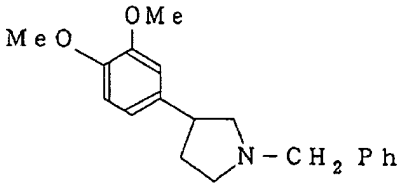
In Eur. J. Med., 27, 407 (1992), a compound represented by the following formula and its binding affinity at dopamine receptor are described:



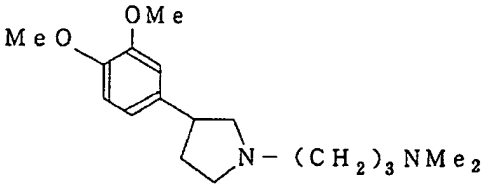
In J. Org. Chem., 58, 36 (1993), a compound represented by the following formula is described, while no description about its physiological activity is provided:



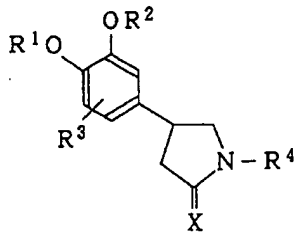
In Swiss Patent No. 526535, a compound represented by the following formula is described as a synthetic intermediate:



In Japanese Second (examined) Patent Publication No. 49-16871, a compound represented by the following formula is described as having antiulcer effect:

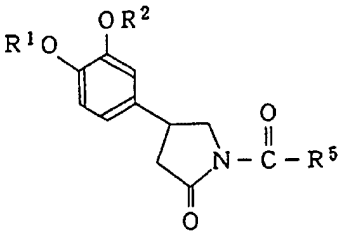


In Japanese First (unexamined) Patent Publication No. 50-157360, a compound represented by the following general formula is described as a treating medicament for neuropsychosis:

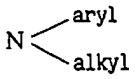


wherein R^1 and R^2 independently represent C_1 - C_5 alkyl; R^3 represents hydrogen or methoxy; R^4 represents hydrogen, alkyl, aryl or acyl; and X represents oxygen or sulfur.

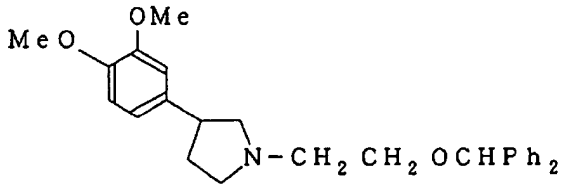
In Japanese Second (examined) Patent Publication No. 61-2660, a compound represented by the following general formula is described as a treating medicament for neuropsychosis:



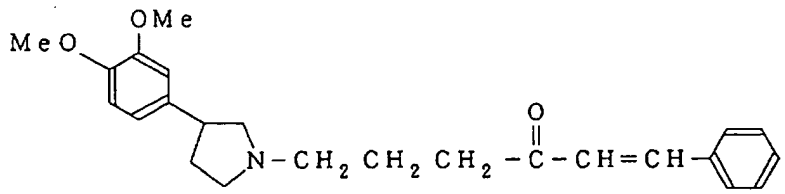
wherein R^1 and R^2 may be the same or different and independently represent C_1 - C_5 alkyl; and R^5 represents C_1 - C_8 O-aralkyl, O-aryl, NH-aryl, NH-aralkyl, N-(alkyl)$_2$, N-(aryl)$_2$ or



In Japanese First (unexamined) Patent Publication No. 2-121964, a compound represented by the following formula is described as having calcium antagonism:

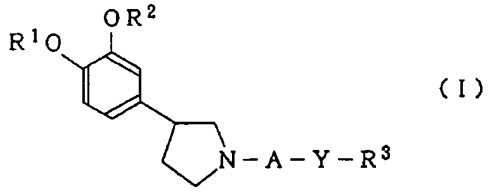


In European Patent No. 344577, a compound represented by the following formula is described as a treating medicament for ischemia heart disease:



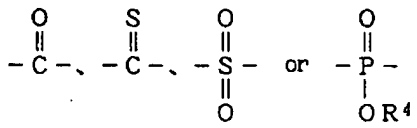
SUMMARY OF THE INVENTION

The present inventors have made researches for providing new compounds showing the inhibition of PDE IV and found out that specific 3-phenylpyrrolidine derivatives have excellent physiological activity, so as to reach completion of the present invention. Specifically, the gist of the present invention resides in a 3-phenylpyrrolidine derivative of the following general formula (I):

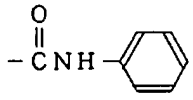


(I)

wherein R^1 represents C_1 - C_4 alkyl; R^2 represents tetrahydrofuranyl, C_1 - C_7 alkyl, C_1 - C_7 haloalkyl, C_2 - C_7 alkenyl, bicyclo [2,2,1] hept-2-yl or C_3 - C_8 cycloalkyl; A represents



wherein R^4 represents C_1 - C_4 alkyl; Y represents -O-, -S-, -O-N=CH-, -NR^5- wherein R^5 represents hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkylcarbonyl or pyridylmethyl, or single bond; and R^3 represents C_1 -C_7 alkyl which is unsubstituted or substituted by one or more substituents, or -$(CH_2)_n$-B wherein n is an integer of from 0 to 4, B represents phenyl which is unsubstituted or substituted by one or more substituents, naphtyl which is unsubstituted or substituted by one or more substituents, or heterocyclic residue which is unsubstituted or substituted by one or more substituents; provided that when -A-Y-R^3 is



R^1 and R^2 are not methyl at the same time.

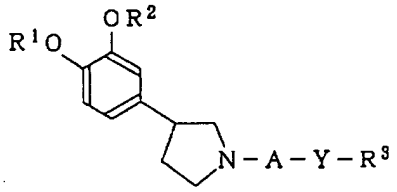
The gist of the present invention further resides in optical isomers, salts, N-oxide derivatives, hydrates and solvates of the foregoing 3-phenylpyrrolidine derivative, and further resides in a pharmaceutical

composition including such a compound as an effective component.

DETAILED DESCRIPTION OF THE INVENTION

Hereinbelow, the present invention will be described in detail.

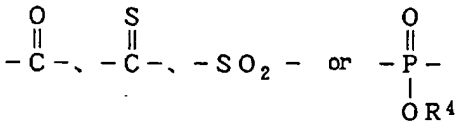
In the following general formula (I):



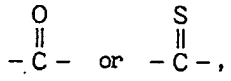
(I)

R^1 represents linear or branched C_1 - C_4 alkyl (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl or the like), preferably methyl or ethyl, and more preferably methyl. R^2 represents tetrahydrofuranyl, linear or branched C_1 - C_7 alkyl (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-butyl, n-pentyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, n-hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methyl pentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, heptyl, 5-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl or the like) , C_1 - C_7 haloalkyl (chloromethyl, bromomethyl, dichloromethyl, 1-chloroethyl, 2-chloroethyl, 3-chloropropyl, 4-chlorobutyl, 5-chloropentyl, 6-chlorohexyl, difluoromethyl, trifluoromethyl or the like), C_2 - C_7 alkenyl (vinyl, allyl, 2-propenyl, isopropenyl, 3-butenyl, 4-pentenyl, 5-hexenyl or the like), bicyclo [2,2,1] hept-2-yl, or C_3 - C_8 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like), preferably tetrahydrofuranyl, C_3 - C_6 alkyl or C_4 - C_6 cycloalkyl, and more preferably cyclopentyl.

A represents



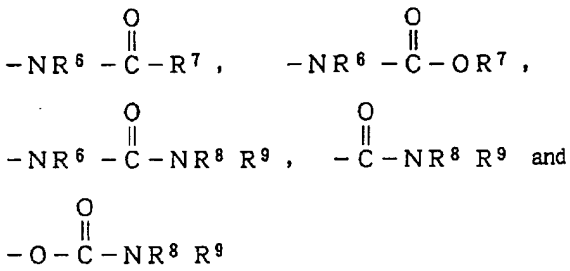
wherein R^4 represents linear or branched C_1 - C_4 alkyl (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl or the like) , preferably



more preferably

Y represents -O-, -S-, -O-N=CH-, -NR^5- where R^5 represents hydrogen, linear or branched C_1 - C_4 alkyl (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl or the like) or pyridylmethyl, or single bond, preferably -O-, -S-, -NR^5- (R^5 is as defined above) or single bond, and more specifically -O- or -NR^5- (R^5 is as defined above).

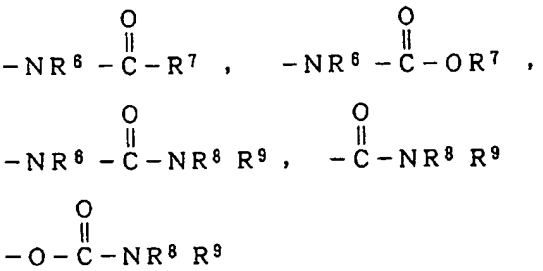
R^3 represents linear or branched C_1 - C_7 alkyl (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl or the like) which is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen (fluorine, chlorine, bromine, iodine or the like), linear or branched C_1 - C_4 alkoxy (methoxy, isopropoxy, butoxy or the like), linear or branched C_1 - C_4 alkylthio (methylthio, isopropylthio, butylthio or the like), linear or branched C_1 - C_4 alkylsulfinyl (methylsulfinyl, isopropylsulfinyl, butylsulfinyl or the like), linear or branched C_1 - C_4 alkylsulfonyl (methylsulfonyl, isopropylsulfonyl, butylsulfonyl or the like), cyano, nitro, amino, hydroxy, carboxy, benzyloxy, C_1 - C_4 acyl (formyl, acetyl, propionyl or the like), C_2 - C_4 alkoxycarbonyl (methoxycarbonyl, ethoxycarbonyl or the like), linear or branched C_1 - C_4 alkylamino (methylamino, isopropylamino, butylamino or the like), linear or branched C_2 - C_6 dialkylamino (dimethylamino, diethylamino or the like), and



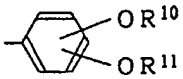
wherein R^6, R^8 and R^9 independently represent hydrogen or linear or branched C_1 - C_4 alkyl (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl or the like) and R^7 represents linear or branched C_1 - C_4 alkyl (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl or the like), and preferably selected from the group consisting of halogen, C_1 - C_4 alkoxy, hydroxy, C_1 - C_4 alkylamino and C_2 - C_6 dialkylamino;

or -(CH2)n -B wherein n is an integer of from 0 to 4, preferably from 0 to 2, and more preferably 1 or 2, and B represents phenyl, naphtyl or heterocyclic residue (thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidyl, piperidino, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, morpholinyl, morpholino, piperazinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, 1,2,3,4-tetrahydroquinoline-2-yl, 5,6,7,8-tetrahydro-1,6-naphthyridine-6-yl, indolyl or the like, which includes 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen and 5 to 10 atoms in total for forming a ring, preferably thienyl, furyl, imidazolyl, pyrazolyl, pyridyl, pyrrolidinyl, piperidyl, piperidino, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazinyl, pyrimidinyl, 1,2,3,4-tetrahydroquinoline-2-yl, 5,6,7,8-tetrahydro-1,6-naphthyridine-6-yl, indolyl, and more preferably pyridyl, piperidyl, piperidino, piperazinyl, pyridazinyl, pyrazinyl, pyrimidinyl or the like, which has a 6-membered ring and includes 1 or 2 nitrogen atoms as hetero atom), and

wherein each of phenyl, naphtyl or heterocyclic residue referred to above is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen (fluorine, chlorine, bromine, iodine or the like), linear or branched C_1 - C_4 alkyl (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl or the like), linear or branched C_1 - C_4 alkoxy (methoxy, isopropoxy, butoxy or the like), linear or branched C_1 - C_4 alkylthio (methylthio, isopropylthio, butylthio or the like), linear or branched C_1 - C_4 alkylsulfinyl (methylsulfinyl, isopropylsulfinyl, butylsulfinyl or the like), linear or branched C_1 - C_4 alkylsulfonyl (methylsulfonyl, isopropylsulfonyl, butylsulfonyl or the like), cyano, nitro, amino, hydroxy, carboxy, C_1 - C_4 acyl (formyl, acetyl, propionyl or the like), C_2 - C_4 alkoxycarbonyl (methoxycarbonyl, ethoxycarbonyl or the like), linear or branched C_1 - C_4 alkylamino (methylamino, isopropylamino, butylamino or the like), linear or branched C_2 - C_6 dialkylamino (dimethylamino, diethylamino or the like),

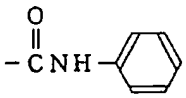


wherein R^5, R^7, R^8 and R^9 are as defined above,



wherein R^{10} represents linear or branched C_1 - C_4 alkyl (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl or the like) and R^{11} represents C_3 - C_8 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like) or linear or branched C_1 - C_4 alkyl (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl or the like),
and pyridyl, and preferably selected from the group consisting of halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, cyano, nitro, amino, hydroxy, phenyl and pyridyl, and
wherein B preferably represents heterocyclic residue which is unsubstituted or substituted by one or more substituents (as defined above), and more preferably heterocyclic residue which is unsubstitured.

In the general formula (I), when -A-Y-R^3 is



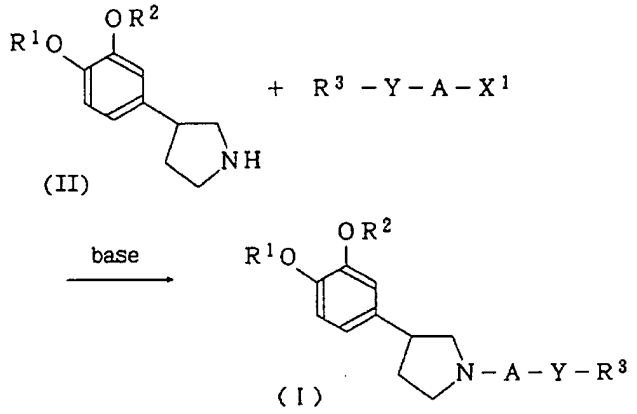
R^1 and R^2 are not methyl at the same time.

When R^3 represents -$(CH_2)_n$-B (n is as defined above) and B is heterocyclic residue having one or more nitrogen atoms as hetero atom, it is possible that the compounds represented by the general formula (I) exist in the form of N-oxide derivatives. On the other hand, it is preferable that salts of the compounds represented by the general formula (I) are physiologically acceptable so that, for example, inorganic acid salts, such as, a hydrochloride, a hydrobromide, a hydroiodide, a sulfate, a phosphate, and organic acid salts, such as, an oxalate, a maleate, a fumarate, a lactate, a malate, a citrate, a tartrate, a benzoate, a methanesulfonate, a p-toluenesulfonate can be enumerated. The compounds of the formula (I), their N-oxide derivatives and their salts can exist in the form of hydrates or solvates. Accordingly, those hydrates and solvates are also included in the compounds of the present invention. As solvents of solvates, methanol, ethanol, isopropanol, acetone, ethyl acetate, methylene chloride and the like can be enumerated.

Further, the compounds of the general formula (I) include asymmetric carbon atoms so that isomers exist. These isomers are also included in the present invention.

The compound of the present invention can be prepared, for example, according to the following method:

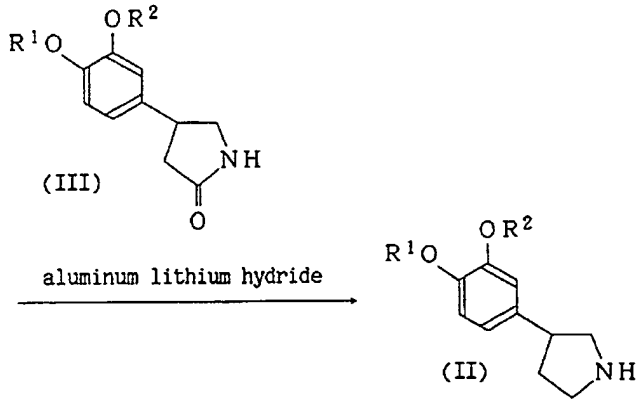
Preparation Method 1



wherein R^1, R^2, R^3, A and Y are as defined before, and X^1 represents halogen.

The reaction is performed at a temperature range from 0 to 150oC in the presence of organic base, such as, triethylamine, pyridine or N,N-diethylaniline or inorganic base, such as, sodium carbonate or sodium hydride, by use of no solvent or in a solvent, for example, ketones, such as, acetone or ethyl methyl ketone, aromatic hydrocarbones, such as, benzene or toluene, ethers, such as, diethyl ether, tetrahydrofuran or dioxane, acetic esters, such as, ethyl acetate or isobutyl acetate, or in an aprotic polar solvent, such as, acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide or N-methylpyrrolidone.

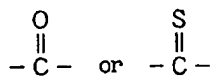
A compound of the general formula (II) which is a starting material of the foregoing reaction can be prepared, for example, according to the following reaction formula from a compound of the following general formula (III) which are prepared according to the method described in Japanese First (unexamined) Patent Publication No. 50-157360 or the like.



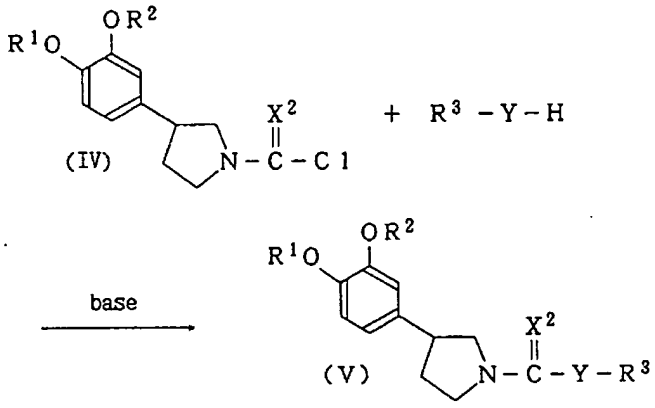
wherein R^1 and R^2 are as defined before.

Preparation Method 2

When A is



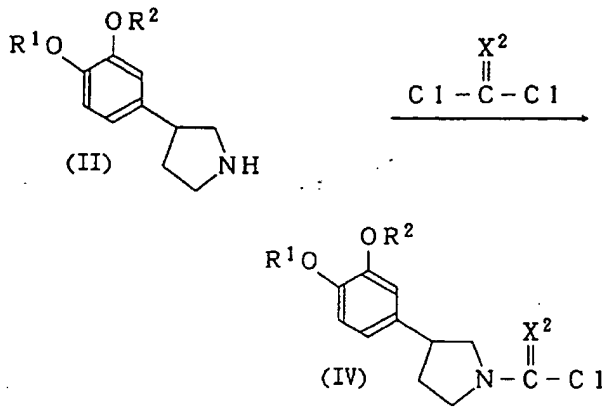
and Y represents -O-, -S-, -O-N=CH- or -NR^5 - (R^5 is as defined before), a compound of the following general formula (V) can also be prepared according to the following method:



wherein R^1, R^2, R^3 and Y are as defined before, and X^2 represents oxygen or sulfur.

The reaction is performed at a temperature range from 0 to 150oC in the presence of organic base, such as, triethylamine, pyridine or N,N-diethylaniline or inorganic base, such as, sodium carbonate or sodium hydride, by use of no solvent or in a solvent, for example, ketones, such as, acetone or ethyl methyl ketone, aromatic hydrocarbones, such as, benzene or toluene, ethers, such as, diethyl ether, tetrahydrofuran or dioxane, acetic esters, such as, ethyl acetate or isobutyl acetate, or in an aprotic polar solvent, such as, acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide or N-methylpyrrolidone.

A compound of the foregoing general formula (IV) which is a starting material of the foregoing reaction can be prepared according to the following reaction formula from the starting material (II) in the preparation method 1.



wherein R^1, R^2 and X^2 are as defined before.

When the compound of the present invention is used as a treating medicament, the compound is dosed single or in combination with a pharmaceutically acceptable carrier. A composition of the carrier is determined based on solubility of the compound, chemical property of the compound, dosage route, dosage schedule and so on.

For example, the compound may be oral-dosed in the form of a granule medicine, a powder medicine, a tablet, a hard capsule medicine, a soft capsule medicine, a sirup medicine, an emulsion medicine, a suspended medicine or a liquid medicine, or may be intravenous-dosed, intramuscular-dosed or subcutaneous-dosed in the form of an injection medicine.

The compound may be powdered for injection and prepared to be used when necessary. The compound of the present invention may be used with pharmaceutical organic or inorganic and solid or liquid carrier or diluent which is suitable for oral, non-oral, through-body or local dosing. As a forming agent to be used when producing the solid medicine, for example, lactose, sucrose, startch, talc, cellulose or dextrin may be used. The liquefied medicines for oral dosing, that is, the emulsion medicine, the sirup medicine, the suspended medicine, the liquid medicine and the like, include the generally used inert diluent, such as, water or vegetable oil. These medicines can contain, other than the inert diluent, an auxiliary agent, such as, a wetting agent, a suspension assisting agent, a sweet agent, an aromatic, a coloring agent or a preserving agent. The liquefied medicine may be contained in a capsule made of a material, such as, gelatin which can be disintegrated in the body. As a solvent or a suspending agent to be used in the course of producing the medicine for non-oral dosing, such as, the medicine for injection, for example, water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate or lecithin can be enumerated. The known method can be used for making up the medicine.

When the compound of the present invention is used for oral dosing, a clinical dosing amount is, in general, 0.01mg to 1000mg per day, and preferably 0.01mg to 100mg, in case of an adult. It is naturally further preferable to properly increase or decrease a dosage amount depending on age, the condition of disease, the condition of patient, presence or absence of simultaneous dosing and so on. In case of the compound of the present invention, the foregoing dosing amount per day may be divided into two or three and dosed with proper intervals, or intermittent dosing may also be allowed.

On the other hand, when using the compound of the present invention as the injection medicine, it is preferable that a one-time dosage amount of 0.001mg to 100mg be continuously or intermittently dosed in case of an adult.

[Embodiment]

Hereinbelow, the present invention will be described in detail in terms of embodiments and test examples. The present invention is not limited to those embodiments and tests.

Embodiment 1

Preparation of 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-pyridylmethylaminocarbonyl) pyrrolidine (Compound No. 22 in Table 1):

216mg of 3-(aminomethyl) pyridine and 202mg of triethylamine were dissoved in 5ml of tetrahydrofuran. During agitation at a cold temperature, a solution obtained by dissolving 545mg of 1-chloroformyl-3-(3-cyclopentyloxy-4-methoxyphenyl) pyrrolidine in 3ml of tetrahydrofuran was added in drops. After dropping, agitation was continued for 6 hours at a room temperature. Thereafter, the agitated solution was poured into ice water and then extracted with ethyl acetate. After organic layers were cleaned by water and dried over magnesium sulfate, it was concentrated under a reduced pressure. The residue was purified by means of the silica gel column chromatography to obtain 432mg of Compound No. 22 in Table 1.

Embodiment 2

Preparation of 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-(ethoxycarbonyl) pyrrolidine (Compound No. 4 in Table 1):

460mg of 3-(3-cyclopentyloxy-4-methoxyphenyl) pyrrolidine and 214mg of triethylamine were dissoved in 15ml of dichloromethane and cooled in an ice bath. During agitation, 229mg of ethyl chloroformate was added in drops. After dropping, agitation was continued for 1 hour at a room temperature. Thereafter, the agitated solution was poured into ice water and then extracted with dichloromethane. After organic layers were cleaned by water and dried over magnesium sulfate, it was concentrated under a reduced pressure. The residue was purified by means of the silica gel column chromatography to obtain 92mg of Compound No. 4 in Table 1.

Embodiment 3

Compounds shown in Table 1 were synthesized according to the methods in Embodiments 1 and 2.

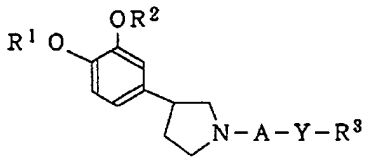


Table 1

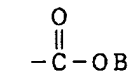
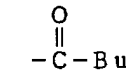
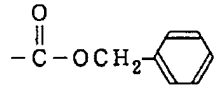
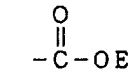
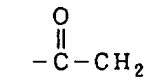
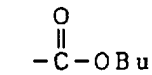
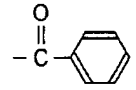
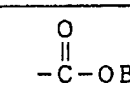
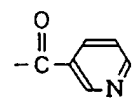
compound No.	R^1	R^2	$-A-Y-R^3$	physical properties
1	Me			oily matter
2	Me			oily matter
3	Me			oily matter
4	Me			oily matter
5	Me			oily matter
6	Me			oily matter
7	Me			oily matter
8	Me			oily matter
9	Me			oily matter

Table 1 (Continued)

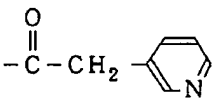
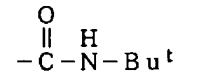
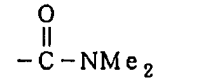
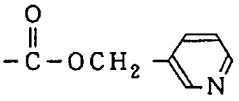
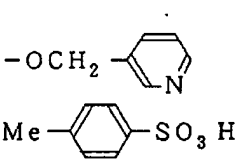
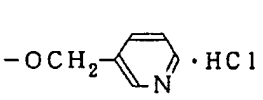
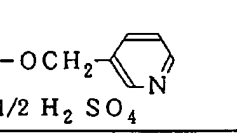
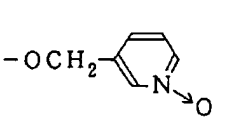
compound No.	R^1	R^2	$-A-Y-R^3$	physical properties
10	Me			oily matter
11	Me			mp 125-126°C
12	Me			oily matter
13	Me			oily matter
14	Me			mp 148-149°C
15	Me			mp 108-114°C
16	Me			mp 142-144°C
17	Me			oily matter

Table 1 (Continued)

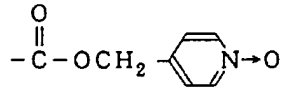
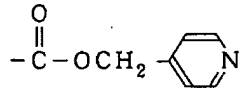
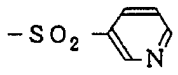
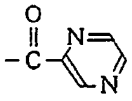
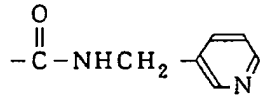
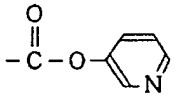
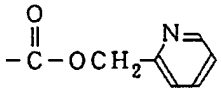
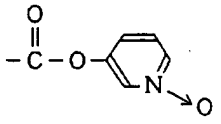
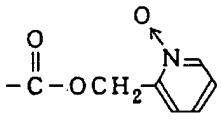
compound No.	R^1	R^2	$-A-Y-R^3$	physical properties
18	Me			amorphous solid
19	Me			oily matter
20	Me			oily matter
21	Me			oily matter
22	Me			m p 129-130°C
23	Me			oily matter
24	Me			oily matter
25	Me			oily matter
26	Me			oily matter

Table 1 (Continued)

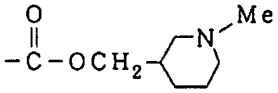
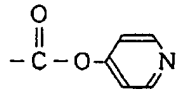
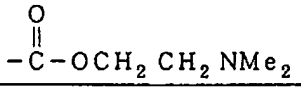
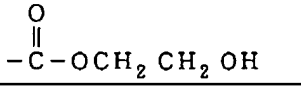
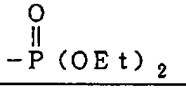
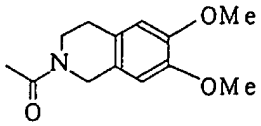
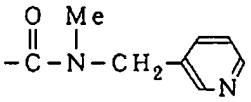
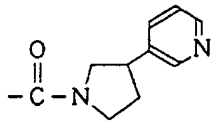
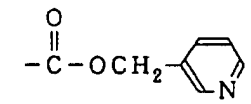
compound No.	R^1	R^2	$-A-Y-R^3$	physical properties
27	Me			oily matter
28	Me			oily matter
29	Me			oily matter
30	Me			oily matter
31	Me			oily matter
32	Me			oily matter
33	Me			oily matter
34	Me			oily matter
35	Me	Me		oily matter

Table 1 (Continued)

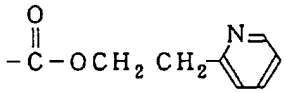
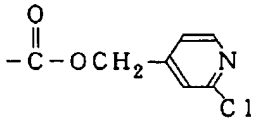
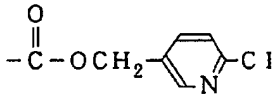
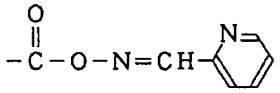
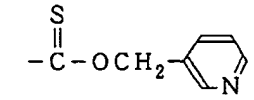
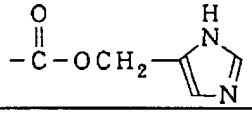
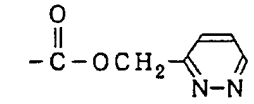
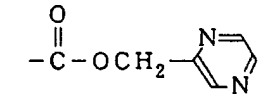
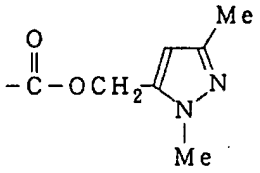
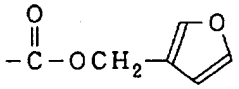
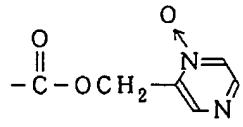
compound No.	R^1	R^2	$-A-Y-R^3$	physical properties
36	Me			oily matter
37	Me			oily matter
38	Me			oily matter
39	Me			oily matter
40	Me			oily matter
41	Me			oily matter
42	Me			oily matter
43	Me			oily matter

Table 1 (Continued)

compound No.	R^1	R^2	$-A-Y-R^3$	physical properties
44	Me			oily matter
45	Me			oily matter
46	Me			oily matter

Hereinbelow, NMR spectra are shown for the following compounds in the form of amorphous solid and oily matter, wherein the compounds are identified by Compound No. in Table 1.

No. 1

^{1}HNMR ($CDCl_3$) δppm: 1.48 (s, 9H), 1.53-1. 69 (m, 2H), 1.73-2.00 (m, 7H), 2.14-2.28 (m , 1H), 3.16-3.86 (m, 5H), 3.83 (s, 3H), 4.70 -4.81 (m, 1H), 6.73-6.85 (m, 3H)

No. 2

^{1}HNMR ($CDCl_3$) δppm: 1.28 (s, 9H), 1.50-1. 68 (m, 2H), 1.73-2.04 (m, 7H), 2.13-2.33 (m , 1H), 3.16-4.10 (m, 5H), 3.83 (s, 3H), 4.71 -4.80 (m, 1H), 6.71-6.85 (m, 3H)

No. 3

^{1}HNMR ($CDCl_3$) δppm: 1.52-1.65 (m, 2H), 1. 76-2.05 (m, 7H), 2.18-2.36 (m, 1H), 3.24-3 .92 (m, 5H), 3.82 (s, 3H), 4.72-4.79 (m, 1H) ,5.16 (s, 2H), 6.74-6.83 (m, 3H), 7.24-7.3 8 (m, 5H)

No. 4

^{1}HNMR ($CDCl_3$) δppm: 1.24-1.31 (m, 3H), 1. 54-1.70 (m, 2H), 1.74-2.04 (m, 7H), 2.18-2 .32 (m, 1H), 3.22-3.90 (m, 5H), 3.83 (s, 3H) , 4.12-4.22 (m, 2H), 4.77 (m, 1H), 6.74-6.8 4 (m, 3H)

No. 5

^{1}HNMR ($CDCl_3$) δppm: 1.08 (brs, 9H), 1.54-2.38 (m, 10H), 2.21 (brs, 2H), 3.22-4.06 (m , 5H), 3.83 (s, 3H), 4.70-4.80 (m, 1H), 6.75 -6.81 (m, 3H)

No. 6

^{1}HNMR ($CDCl_3$) δppm: 0.90-0.98 (m, 3H), 1. 34-2.04 (m, 13H), 2.18-2.32 (m, 1H), 3.24-3.92 (m, 5H), 3.82 (s, 3H), 4.08-4.13 (m, 2H), 4.76 (m, 1H), 6.74-6.83 (s, 3H)

No. 7

^{1}HNMR ($CDCl_3$) δppm: 1.56-1.70 (m, 2H), 1. 76-2.42 (m, 8H), 3.24-3.94 (m, 5H), 3.83 (b rs, 3H), 4.70-4.80 (m, 1H), 6.71-6.82 (m, 3 H), 7.38-7.43 (m, 3H), 7.54-7.56 (m, 2H)

No. 8

^{1}HNMR ($CDCl_3$) δppm: 1.48 (s, 9H), 1.80-2. 28 (m, 4H), 3.15-4.09 (m, 9H), 3.84 (s, 3H), 4.89-5.00 (m, 1H), 6.73 (brs, 1H), 6.84 (br s, 2H)

No. 9

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.44 (m, 10H), 3 .28-4.16 (m, 5H), 3.82 and 3.84 (a pair of s, 3H), 4.72-4.80 (m, 1H), 6.70-6.83 (m , 3H), 7.32-7.40 (m, 1H), 7.86-7.92 (m, 1H) , 8.64-8.69 (m, 1H), 8.81 (m, 1H)

No. 10

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.42 (m, 10H), 3 .26-4.08 (m, 5H), 3.66 (brs. 2H), 3.83 (brs , 3H), 4.75 (m, 1H), 6.72-6.84 (m, 3H), 7.24 -7.30 (m, 1H), 7.68-7.74 (m, 1H), 8.50-8.5 2 (m, 2H)

No. 12

^{1}HNMR ($CDCl_3$) δppm: 1.53-1.68 (m, 2H), 1. 75-2.00 (m, 7H), 2.15-2.28 (m, 1H), 2.85 (s , 6H), 3.18-3.31 (m, 1H), 3.39 (t, 1H, J=9Hz), 3.46-3.61 (m, 2H), 3.70 (d-d, 1H, J=7 an d 9Hz), 3.83 (s, 3H), 4.71-4.80 (m, 1H), 6. 74-6.84 (m, 3H)

No. 13

^{1}HNMR ($CDCl_3$) δppm: 1.51-1.70 (m, 2H), 1. 75-2.04 (m, 7H), 2.18-2.34 (m, 1H), 3.23-3 .53 (m, 3H), 3.58-3.96 (m, 2H), 3.83 (s, 3H) , 4.68-4.80 (m, 1H), 5.18 (s, 2H), 6.70-6.8 4 (m, 3H), 7.26-7.35 (m, 1H), 7.73 (m, 1H), 8 .57 (m, 1H), 8.65 (m, 1H)

No. 17

^{1}HNMR ($CDCl_3$) δppm: 1.51-1.70 (m, 2H), 1. 75-2.09 (m, 7H), 2.20-2.35 (m, 1H), 3.25-3 .53 (m, 3H), 3.63-3.75 (m, 1H), 3.80-3.93 (m, 1H), 3.83 (s, 3H), 4.71-4.81 (m, 1H), 5.1 3 (brs, 2H), 6.70-6.86 (m, 3H), 7.27 (m, 2H) , 8.16 (m, 1H), 8.28 (m, 1H)

No. 18

^{1}HNMR ($CDCl_3$) δppm: 1.54-2.08 (m, 9H), 2. 22-2.36 (m, 1H), 3.28-3.92 (m, 5H), 3.83 (s , 3H), 4.76 (m, 1H), 5.12 (brs, 2H), 6.75-6. 84 (m, 3H), 7.27-7.32 (m, 2H), 8.17-8.21 (m , 2H)

No. 19

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.12 (m, 9H), 2. 24-2.36 (m, 1H), 3.30-3.90 (m, 5H), 3.83 (s , 3H), 4.77 (m, 1H), 5.19 (brs, 2H), 6.76-6. 86 (m, 3H), 7.26-7.30 (m, 2H), 8.57-8.61 (m , 2H)

No. 20

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.06 (m, 9H), 2. 14-2.28 (m, 1H), 3.16-3.90 (m, 5H), 3.81 (s , 3H), 4.68-4.76 (m, 1H), 6.61-6.78 (m, 3H) , 7.48-7.56 (m, 1H), 8.13-8.16 (m, 1H), 8.9 4 (brs, 1H), 9.10 (brs, 1H)

No. 21

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.16 (m, 9H), 2. 30-2.40 (m, 1H), 3.30-3.48 (m, 1H), 3.64-4 .26 (m, 4H), 3.83 (brs, 3H), 4.74-4.80 (m, 1 H), 6.77-6.83 (m, 3H), 8.52-8.56 (m, 1H), 8 .62-8.66 (m, 1H), 9.17 (s, 1H)

No. 23

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.18 (m, 9H), 2. 26-2.42 (m, 1H), 3.34-4.16 (m, 5H), 3.83 (s , 3H), 4.72-4.80 (m, 1H), 6.78-6.88 (m, 3H) , 7.32 (m, 1H), 7.55-7.80 (m, 1H), 8.47 (m, 2 H)

No. 24

^{1}HNMR ($CDCl_3$) δppm: 1.50-1.70 (m, 2H), 1. 73-2.04 (m, 7H), 2.20-2.35 (m, 1H), 3.25-3 .59 (m, 3H), 3.66-3.78 (m, 1H), 3.83 (s, 3H) , 3.86-3.96 (m, 1H), 4.70-4.79 (m, 1H), 5.2 8 (brs, 2H), 6.71-6.84 (m, 3H), 7.16-7.26 (m, 1H), 7.39 (t, 1H, J = 7Hz), 7.65-7.74 (m, 1 H), 8.58 (m, 1H), 8.65 (m, 1H)

No. 25

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.16 (m, 9H), 2. 28-2.44 (m, 1H), 3.34-4.06 (m, 5H), 3.84 (s , 3H), 4.74-4.80 (m, 1H), 6.77-6.83 (m, 3H) , 7.23-7.27 (m, 2H), 8.06-8.09 (m, 1H), 8.1 9 (s, 1H)

No. 26

^{1}HNMR ($CDCl_3$) δppm: 1.50-1.70 (m, 2H) 1.7 5-2.10 (m, 7H), 2.22-2.40 (m, 1H), 3.30-3. 62 (m, 3H), 3.68-3.83 (m, 1H), 3.84 (s, 3H), 3.89-4.00 (m, 1H), 4.70-4.81 (m, 1H), 5.44 (brs, 2H), 6.74-6.86 (m, 3H), 7.20-7.35 (m , 2H), 7.36-7.45 (m, 1H), 8.25 (m, 1H)

No. 27 (diastereo mixture)

^{1}HNMR ($CDCl_3$) δppm: 1.52-2.40 (m, 17H), 2 .27 and 2.29 (a pair of s, 3H), 2.78-2. 94 (m, 2H), 3.24-4.08 (m, 7H), 3.83 (s, 3H), 4.72-4.80 (m, 1H), 6.75-6.86 (m, 3H)

No. 28

^{1}HNMR ($CDCl_3$) δppm: 1.56-1.72 (m, 2H), 1. 76-1.94 (m, 6H), 2.04-2.16 (m, 1H), 2.33-2 .42 (m, 1H), 3.34-3.93 (m, 5H), 3.83 (s, 3H) , 4.73-4.80 (m, 1H), 6.32-6.38 (m, 2H), 6.7 5-6.86 (m, 3H), 7.72-7.77 (m, 2H)

No. 29

^{1}HNMR ($CDCl_3$) δppm: 1.51-1.69 (m, 2H), 1. 74-2.01 (m, 7H), 2.15-2.30 (m, 1H), 2.29 (s , 3H), 2.31 (s, 3H), 2.60 (m, 2H), 3.22-3.50 (m, 3H), 3.57-3.72 (m, 1H), 3.75-3.91 (m, 1 H), 3.82 (s, 3H), 4.22 (t, 2H, J = 5Hz), 4.70-4.80 (m, 1H), 6.71-6.84 (m, 3H)

No. 30

^{1}HNMR ($CDCl_3$) δppm: 1.51-1.69 (m, 2H), 1. 74-2.05 (m, 7H), 2.19-2.34 (m, 1H), 2.80 (b rs, 1H), 3.23-3.74 (m, 7H), 3.83 (s, 3H), 4. 23-4.31 (m, 2H), 4.70-4.81 (m, 1H), 6.72-6 .85 (m, 3H)

No. 31

^{1}HNMR ($CDCl_3$) δppm: 1.30-1.37 (m, 6H), 1. 54-1.68 (m, 2H), 1.78-2.04 (m, 7H), 2.20-2 .32 (m, 1H), 3.10-3.18 (m, 1H), 3.24-3.50 (m, 3H), 3.60-3.68 (m, 1H), 3.83 (s, 3H), 4.0 0-4.16 (m, 4H), 4.72-4.80 (m, 1H), 6.75-6. 83 (m, 3H)

No. 32

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.06 (m, 9H), 2. 18-2.30 (m, 1H), 2.72-2.96 (m, 2H), 3.24-3 .92 (m, 7H), 3.83 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.40 (s, 2H), 4.72-4.80 (m, 1H), 6. 59 (s, 1H), 6.62 (s, 1H), 6.77-6.86 (s, 3H)

No. 33

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.06 (m, 9H), 2. 16-2.32 (m, 1H), 2.81 (s, 3H), 3.22-3.36 (m , 1H), 3.43 (t, 1H, J=9Hz), 3.54-3.60 (m, 2H), 3.72-3.81 (m, 1H), 3.83 (s, 3H), 4.43 (d, 1H, J=12Hz), 4.50 (d, 1H, J=12Hz), 4.72-4. 80 (m, 1H), 6.75-6.84 (m, 3H), 7.25-7.30 (m , 1H), 7.68-7.71 (m, 1H), 8.52-8.56 (m, 2H)

No. 34 (diastereo mixture)

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.08 (m, 10H), 2 .18-2.36 (m, 2H), 3.20-3.94 (m, 10H), 3.83 (s, 3H), 4.72-4.80 (m, 1H), 6.76-6.84 (m, 3 H), 7.16-7.19 (m, 2H), 8.53-8.55 (m, 2H)

No. 35

^{1}HNMR ($CDCl_3$) δppm: 1.90-2.10 (m, 1H), 2. 19-2.33 (m, 1H), 3.24-3.51 (m, 3H), 3.60-3 .95 (m, 2H), 3.87 (s, 6H), 5.18 (brs, 2H), 6. 70-6.86 (m, 3H), 7.27-7.34 (m, 1H), 7.68-7 .76 (m, 1H), 8.57 (m, 1H), 8.65 (m, 1H)

No. 36

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.06 (m, 9H), 2. 16-2.28 (m, 1H), 3.12-3.88 (m, 7H), 3.83 (s , 3H), 4.48 (t, 2H, J=7Hz), 4.75 (m, 1H), 6.7 2-6.83 (m, 3H), 7.10-7.24 (m, 2H), 7.54-7. 64 (m, 1H), 8.54 (m, 1H)

No. 37

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.12 (m, 9H), 2. 22-2.38 (m, 1H), 3.50-3.58 (m, 3H), 3.68-3 .94 (m, 2H), 3.83 (s, 3H), 4.77 (m, 1H), 5.16 (brs, 2H), 6.76-6.85 (m, 3H), 7.12-7.21 (m , 1H), 7.31-7.33 (m, 1H), 8.34-8.38 (m, 1H)

No. 38

^{1}HNMR ($CDCl_3$) δppm: 1.51-1.68 (m, 2H), 1. 73-2.04 (m, 7H), 2.19-2.33 (m, 1H), 3.23-3 .52 (m, 3H), 3.57-3.92 (m, 2H), 3.83 (s, 3H) , 4.70-4.80 (m, 1H), 5.15 (brs, 2H), 6.70-6 .84 (m, 3H), 7.29-7.36 (m, 1H), 7.67-7.74 (m, 1H), 8.42 (m, 1H)

No. 39

^{1}HNMR ($CDCl_3$) δppm: 1.50-1.71 (m, 2H), 1. 74-2.11 (m, 7H), 2.23-2.40 (m, 1H), 3.30-3 .64 (m, 3H), 3.70-3.85 (m, 1H), 3.84 (s, 3H) , 3.90-4.05 (m, 1H), 4.71-4.83 (m, 1H), 6.7 3-6.85 (m, 3H), 7.33 (t, 1H, J=9Hz), 7.76 (t , 1H, J=9Hz), 8.14 (d, 1H, J=9Hz), 8.43 (d, 1 H, J=9Hz), 8.64 (brs, 1H)

No. 40

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.16 (m, 9H), 2. 28-2.42 (m, 1H), 3.32-4.28 (m, 5H), 3.83 (b rs, 3H), 4.72-4.78 (m, 1H), 5.56 and 5.57 (a pair of s, 2H), 6.71-6.84 (m, 3H), 7.2 6-7.34 (m, 1H), 7.72-7.76 (m, 1H), 8.54-8. 62 (m, 1H), 8.65-8.69 (m, 1H)

No. 41

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.18 (m, 9H), 2. 32-2.42 (m, 1H), 3.32-3.46 (m, 1H), 3.54-3 .66 (m, 1H), 3.72-3.90 (m, 2H), 3.83 (s, 3H) , 3.94-4.06 (m, 1H), 4.48 (brs, 1H), 4.60 (s , 2H), 4.72-4.80 (m, 1H) 6.75-6.85 (m, 3H), 7.28-7.30 (m, 1H), 8.02 (s, 1H)

No. 42

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.08 (m, 9H), 2. 22-2.36 (m, 1H), 3.26-3.56 (m, 3H), 3.66-3 .96 (m, 2H), 3.83 (s, 3H), 4.72-4.80 (m, 1H) , 5.50 and 5.51 (a pair of s, 2H), 6.75-6.84 (m, 3H), 7.46-7.53 (m, 1H), 7.58-7.66 (m, 1H), 9.14-9.16 (m, 1H)

No. 43

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.10 (m, 9H), 2. 20-2.36 (m, 1H), 3.28-3.56 (m, 3H), 3.70-3 .96 (m, 2H), 3.83 (s, 3H), 4.77 (m, 1H), 5.32 and 5.33 (a pair of s, 2H), 6.75-6.84 (m, 3H), 8.53-8.56 (m, 2H), 8.70-8.71 (m, 1H)

No. 44

^{1}HNMR ($CDCl_3$) δppm: 1.50-1.70 (m, 2H), 1. 74-2.04 (m, 7H), 2.18-2.40 (m, 1H), 2.24 (b rs, 3H), 3.22-3.92 (m, 5H), 3.82 (brs, 6H), 4.70-4.80 (m, 1H), 5.10 (brs, 2H), 6.08 (br s, 1H), 6.69-6.84 (m, 3H)

No. 45

^{1}HNMR ($CDCl_3$) δppm: 1.50-1.69 (m, 2H), 1. 75-2.03 (m, 7H), 2.18-2.30 (m, 1H), 3.23-3 .93 (m, 5H), 3.82 (s, 3H), 4.70-4.80 (m, 1H) , 5.02 (brs, 2H), 6.46 (m, 1H), 6.70-6.84 (m , 3H), 7.39 (m, 1H), 7.48 (m, 1H)

No. 46

^{1}HNMR ($CDCl_3$) δppm: 1.56-2.12 (m, 9H), 2. 22-2.38 (m, 1H), 3.30-3.58 (m, 3H), 3.68-3 .96 (m, 2H), 3.84 (s, 3H), 4.74-4.80 (m, 1H) , 5.27 (brs, 2H), 6.76-6.85 (m, 3H), 8.02 (m , 1H), 8.17-8.19 (m, 1H), 8.41-8.43 (m, 1H)

Embodiment 4

Preparation of (+)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-pyridylmethoxycarbonyl) pyrrolidine and (-)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-pyridylmethoxycarbonyl) pyrrolidine:

145mg of (±)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-pyridylmethoxycarbonyl) pyrrolidine (Compound No. 13 in Table 1) was separated with HPLC (eluent: ethanol/hexane = 10/90) using the optical isomer separation column CHIRALPAKAS (Daicel xxx) to obtain (+)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-pyridylmethoxycarbonyl) pyrrolidine (Compound No. 47) 64mg $[\alpha]D^{25}$ = +22.3° (c0.91, methanol), and (-)-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-pyrid ylmethoxycarbonyl) pyrrolidine (Compound No. 48) 61mg $[\alpha]D^{25}$ = -23.7° (c1.02, methanol).

Embodiment 5

Compounds shown in Table 1 (shown hereinbelow) were synthesized according to the methods in Embodiments 1 and 2.

Table 1 (Continued)

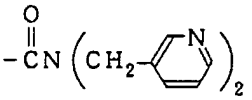
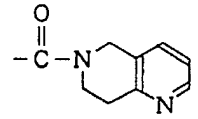
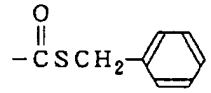
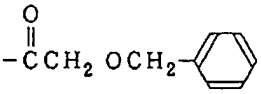
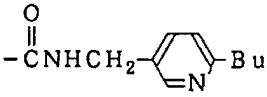
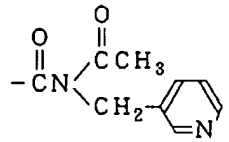
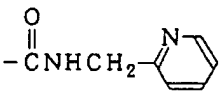
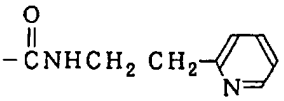
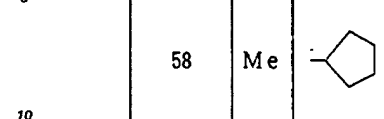
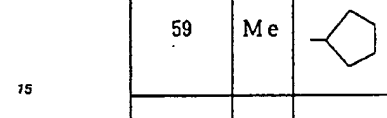
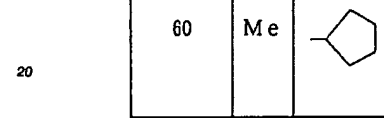
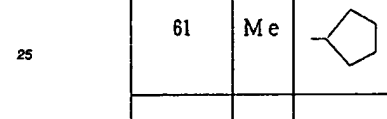
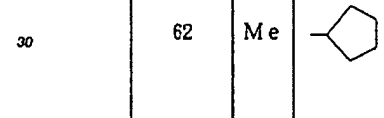
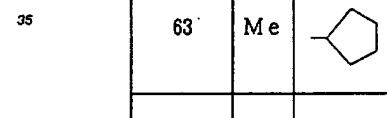
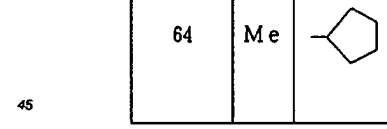
compound No.	R^1	R^2	$-A-Y-R^3$	physical properties
49	Me			oily matter
50	Me			oily matter
51	Me			oily matter
52	Me			oily matter
53	Me			oily matter
54	Me			oily matter
55	Me			oily matter
56	Me			oily matter
57	Me			oily matter

Table 1 (Continued)

compound No.	R^1	R^2	$-A-Y-R^3$	physical properties
58	Me			mp 120-123°C
59	Me			oily matter
60	Me			oily matter
61	Me			mp 93-95°C
62	Me			oily matter
63	Me			amorphous solid
64	Me			amorphous solid

In Table 1, Me represents methyl, Et ethyl, Bun n-butyl and But tert-butyl.

No. 49

^{1}HNMR ($CDCl_3$) δppm: 1.50-2.10 (m, 9H), 2. 20-2.38 (m, 1H), 3.2-3.7 (m, 4H), 3.8 (m, 1H), 3.82 (s, 3H), 4.23-4.57 (m, 4H), 4.60-4. 83 (m, 1H), 6.63-6.93 (m, 3H), 7.20-7.40 (m , 2H), 7.57-7.76 (m, 2H), 8.40-8.68 (m, 4H)

No. 50

^{1}HNMR ($CDCl_3$) δppm: 1.49-2.10 (m, 9H), 2. 20-2.36 (m, 1H), 2.9-3.8 (m, 9H), 3.83 (s, 3 H), 4.73 (s, 2H), 4.70-4.80 (m, 1H), 6.70-6 .85 (m, 3H), 6.80 (dd, 1H), 7.41 (d, 1H), 8.4 3 (d, 1H)

No. 51

^{1}HNMR ($CDCl_3$) δppm: 1.49-1.71 (m, 2H), 1. 74-2.09 (m, 7H), 2.20-2.36 (m, 1H), 3.2-4. 1 (m, 5H), 3.82 (s, 3H), 4.20 (s, 2H), 4.69-4 .79 (m, 1H), 6.69-6.84 (m, 3H), 7.19-7.41 (m, 5H)

No. 52

^{1}HNMR ($CDCl_3$) δppm: 1.53-1.70 (m, 2H), 1. 75-2.08 (m, 7H), 2.20-2.38 (m, 1H), 3.2-4. 1 (m, 5H), 3.82 (s, 3H), 4.13 (m, 2H), 4.65 (m , 2H), 4.70-4.80 (m, 1H), 6.70-6.85 (m, 3H) , 7.25-7.43 (m, 5H)

No. 53

^{1}HNMR ($CDCl_3$) δppm: 0.94 (t, 3H), 1.39 (m, 2H), 1.51-2.09 (m, 11H), 2.23-2.35 (m, 1H) , 2.77 (t, 2H), 3.25-3.48 (m, 3H), 3.55-3.6 6 (m, 1H), 3.8 (m, 1H), 3.83 (s, 3H), 4.44 (d, 2H), 4.53 (t, 1H), 4.69-4.79 (m, 1H), 6.73-6.85 (m, 3H), 7.11 (d, 1H), 7.60 (dd, 1H), 8. 44 (d, 1H)

No. 54

^{1}HNMR ($CDCl_3$) δppm: 1.53-1.70 (m, 2H), 1. 75-2.08 (m, 7H), 2.19-2.35 (m, 1H), 3.00 (m , 3H), 3.20-3.51 (m, 5H), 3.55-3.90 (m, 2H) , 3.83 (s, 3H), 4.57 (m, 2H), 4.70-4.81 (m, 1 H), 6.70-6.85 (m, 3H)

No. 55

^{1}HNMR ($CDCl_3$) δppm: 1.52-1.74 (m, 2H), 1. 75-2.07 (m, 7H), 2.17 (s, 3H), 2.20-2.38 (m , 1H), 3.1-3.9 (m, 5H), 3.83 (s, 3H), 4.63-4 .93 (m, 3H), 6.54-6.84 (m, 3H), 7.27 (m, 1H) , 7.75 (m, 1H), 8.47-8.63 (m, 2H)

No. 56

^{1}HNMR ($CDCl_3$) δppm: 1.47-1.74 (m, 2H), 1. 74-2.10 (m, 7H), 2.18-2.37 (m, 1H), 3.18-3 .53 (m, 3H), 3.58-3.94 (m, 2H), 3.80 (s, 3H) , 4.54 (d, 2H), 4.70-4.80 (m, 1H), 5.84 (t, 1 H), 6.73-6.83 (m, 3H), 7.15 (m, 1H), 7.30 (m , 1H), 7.62 (m, 1H), 8.49 (m, 1H)

No. 57

^{1}HNMR ($CDCl_3$) δppm: 1.50-1.70 (m, 2H), 1. 72-2.04 (m, 7H), 2.18-2.34 (m, 1H), 3.01 (t , 2H), 3.22-3.85 (m, 7H), 3.83 (s, 3H), 4.68 -4.79 (m, 1H), 5.34 (t, 1H), 6.73-6.83 (m, 3 H), 7.08-7.20 (m, 2H), 7.57-7.64 (m, 1H), 8 .50 (m, 1H)

No. 59

^{1}HNMR ($CDCl_3$) δppm: 1.47-2.15 (m, 9H), 2. 22-2.42 (m, 1H), 3.28-4.03 (m, 5H), 3.83 (s , 3H), 4.70-4.80 (m, 1H), 6.61 (bs, 1H), 6.7 5-6.85 (m, 3H), 7.22 (m, 1H), 8.09 (m, 1H), 8 .24 (m, 1H), 8.48 (m, 1H)

No. 60

^{1}HNMR ($CDCl_3$) δppm: 1.48-1.70 (m, 2H), 1. 70-2.05 (m, 7H), 2.16-2.33 (m, 1H), 2.98 (t , 2H), 3.16-3.33 (m, 3H), 3.45-3.75 (m, 4H) , 3.81 (s, 3H), 4.37 (t, 1H), 4.70-4.80 (m, 1 H), 6.65-6.95 (m, 3H), 7.00 (m, 1H), 7.06-7 .23 (m, 2H), 7.35 (m, 1H), 7.62 (m, 1H), 8.67 (bs, 1H)

No. 62

^{1}HNMR ($CDCl_3$) δppm: 1.50-1.70 (m, 2H), 1. 75-2.05 (m, 7H), 2.18-2.35 (m, 1H), 2.81 (t , 2H), 3.23-3.55 (m, 6H), 3.59 (s, 3H), 3.70 -3.87 (m, 1H), 3.83 (s, 3H), 4.45 (t, 1H), 4. 70-4.80 (m, 1H), 5.92 (m, 1H), 6.05 (m,

1H), 6.57 (m, 1H), 6.73-6.83 (m, 3H)

No. 63

^{1}HNMR ($CDCl_3$) δppm: 1.52-1.70 (m, 2H), 1. 74-2.07 (m, 7H), 2.18-2.39 (m, 1H), 3.3-3. 8 (m, 5H), 3.83 (s, 3H), 4.56 (m, 1H), 4.63 (d , 2H), 4.70-4.80 (m, 1H), 6.73-6.83 (m, 3H) , 6.92-7.00 (m, 2H), 7.22 (m, 1H)

No. 64

^{1}HNMR ($CDCl_3$) δppm: 1.53-1.72 (m, 2H), 1. 75-2.23 (m, 7H), 2.30-2.47 (m, 1H), 3.47-3 .66 (m, 3H), 3.79 (m, 1H), 3.84 (s, 3H), 3.98 (m, 1H), 4.73-4.83 (m, 1H), 6.27 (bs, 1H), 6 .78-6.86 (m, 3H), 8.48 (s, 2H)

Hereinbelow, compounds which can be synthesized according to the methods of Embodiments 1 and 2 will be shown in Table 2.

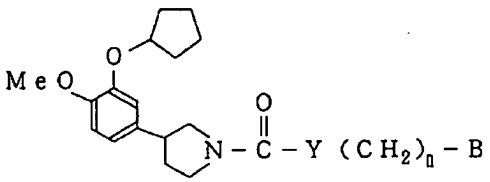


Table 2

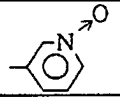
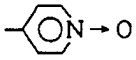
compound No.	Y	n	B
65	-O-	2	
66	-O-	2	
67	-O-	2	
68	-O-	2	
69	-O-	2	
70	-NH-	1	
71	-NH-	2	
72	-NH-	2	
73	-NMe-	1	

Table 2 (Continued)

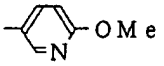
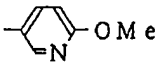
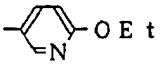
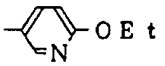
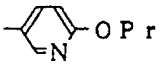
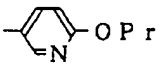
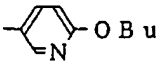
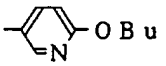
compound No.	Y	n	B
74	-NMe-	1	
75	-NMe-	2	
76	-NMe-	2	
77	-NMe-	2	
78	-O-	1	
79	-O-	2	
80	-O-	1	
81	-O-	2	
82	-O-	1	
83	-O-	2	
84	-O-	1	
85	-O-	2	

Table 2 (Continued)

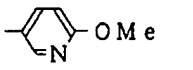
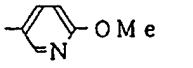
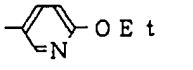
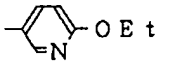
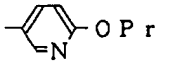
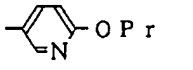
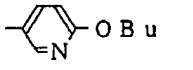
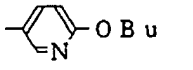
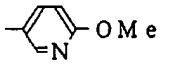
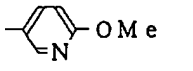
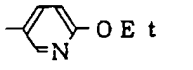
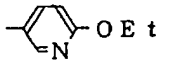
compound No.	Y	n	B
86	-NH-	1	
87	-NH-	2	
88	-NH-	1	
89	-NH-	2	
90	-NH-	1	
91	-NH-	2	
92	-NH-	1	
93	-NH-	2	
94	-NMe-	1	
95	-NMe-	2	
96	-NMe-	1	
97	-NMe-	2	

Table 2 (Continued)

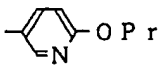
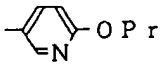
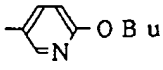
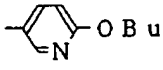
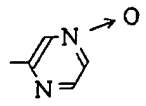
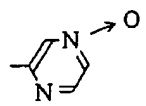
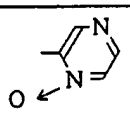
compound No.	Y	n	B
98	-NMe-	1	
99	-NMe-	2	
100	-NMe-	1	
101	-NMe-	2	
102	-O-	2	
103	-O-	1	
104	-O-	2	
105	-O-	2	
106	-O-	1	
107	-O-	2	
108	-O-	2	

Table 2 (Continued)

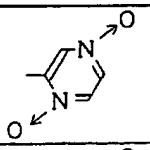
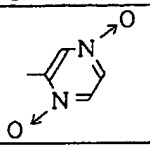
compound No.	Y	n	B
109	-O-	1	
110	-O-	2	
111	-O-	1	
112	-O-	2	
113	-O-	1	
114	-O-	2	
115	-O-	1	
116	-O-	2	
117	-NH-	1	
118	-NH-	2	
119	-NH-	1	

Table 2 (Continued)

compound No.	Y	n	B
120	-NH-	2	
121	-NH-	1	
122	-NH-	2	
123	-NH-	1	
124	-NH-	2	
125	-NH-	1	
126	-NH-	2	
127	-NH-	1	
128	-NH-	2	
129	-NMe-	1	
130	-NMe-	2	
131	-NMe-	1	

Table 2 (Continued)

compound No.	Y	n	B
132	-NMe-	2	
133	-NMe-	1	
134	-NMe-	2	
135	-NMe-	1	
136	-NMe-	2	
137	-NMe-	1	
138	-NMe-	2	
139	-NMe-	1	
140	-NMe-	2	

In Table 2, Me represents methyl, Et ethyl, Pr propyl and Bu butyl.

Embodiment 6

Preparation of Tablet:

1000g of well crushed 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-pyridylmethoxycarbonyl) pyrrolidine hydrochloride (Compound No. 15 in Table 1), 5900g of lactose, 2000g of crystal cellulose, 1000g of low-degree substitution hydroxypropylcellulose and 100g of magnesium stearate are well mixed so as to produce bare tablets containing 10mg of the foregoing compound in one tablet of 100mg using the direct tablet making method. By applying sugar-coating or film-coating to the bare tablets, the sugar-coated tablets or the film-coated tablets were produced.

Embodiment 7

Preparation of Capsule Medicine

1000g of well crushed 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-pyridylmethoxycarbonyl) pyrrolidine p-toluenesulfonate (Compound No. 14 in Table 1), 3000g of corn starch, 6900g of lactose, 1000g of crystal cellulose and 100g of magnesium stearate were mixed to produce capsule medicine containing 10mg of the foregoing compound in one capsule of 120mg.

Embodiment 8

Preparation of Inhalation Medicine

5g of well crushed 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-pyridylmethylaminocarbonyl) pyrrolidine (Compound No. 22 in Table 1), 10g of medium-chain saturated fatty acid triglyceride and 0.2g of (sorbitan xxx) were well mixed. Subsequently, a mixture of 15. 2mg was weighed into each aluminum container of 5ml for aerosol. Further, a mixture of freon 12 and 114, in the ratio of 1:1, of 84.8mg at a low temperature was filled into each container. Thereafter, an adaptor for metering 10.0ml per injection was attached to the container to produce inhalation medicine containing 5mg of the foregoing compound in one spray-type container of 5ml. For showing availability of the compounds of the present invention, the results of the pharmacological tests of the compounds will be given hereinbelow.

(roliplum xxx) in Table 3 is the compound represented by the foregoing structure as described in the foregoing Japanese First Patent Publication No. 50-157360. In, for example, Adv. Second Messenger Phosphoprotein Res., 22, 1 (1988), it is described to show specific inhibition to PDE IV.

Test 1

Action to Phosphodiesterase (PDE) IV Enzyme Activities

Enzyme was partialy purified from human histiocytic lymphoma(U937) cytoplasm fraction by means of the Q-sepharose column according to the method of Nicholson and collaborators [Br. J. Pharmacol., 97, 889 (1989)], and was reacted in a solution of 0.1mg/ml BSA (bovine serum albumin), 1mM EDTA (ethylenediaminetetra acetic acid), 5mM $MgCl_2$ and 50mM Tris-buffer (pH 8.0) for 15 minutes at 30°C using 0.4μM ^{3}H-cAMP as substrate accodring to the method of Hidaka and collaborators [Biochem. Med., 10, 301 (1974)]. ^{3}H-5'-AMP generated was separated by means of the cation exchange column, and the enzyme activity was determined by measuring a radioactivity amont.

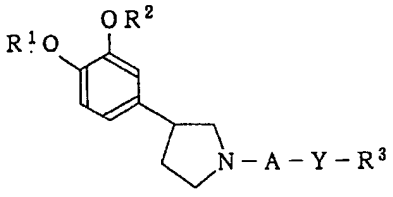
A test compound was added. After incubations for 15 minutes at 30°C, the substrate was added. Inhibition ratios were derived for respective concentrations assuming that the reaction without the test compound was 100%. By using the probit analysis, the concentration (IC_{50}) showing the inhibition rate of 50% was derived. The results are shown in Table 3.

Table 3

compound No.	PDE IV inhibitory activity IC_{50} (M)
1	1.0×10^{-8}
3	6.0×10^{-9}
4	1.1×10^{-8}
6	6.0×10^{-9}
7	2.0×10^{-8}
8	1.9×10^{-8}
13	3.3×10^{-9}
17	2.3×10^{-8}
19	3.8×10^{-9}
23	1.4×10^{-8}
24	2.3×10^{-9}
26	8.8×10^{-9}
32	2.5×10^{-8}
36	1.1×10^{-8}
37	1.9×10^{-8}
38	2.3×10^{-8}
40	1.0×10^{-8}
42	8.0×10^{-9}
48	1.1×10^{-9}
roliplam	3.0×10^{-7}

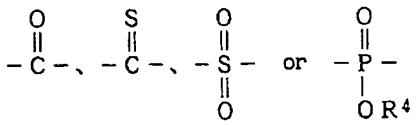
Claims

1. A 3-phenylpyrrolidine derivative of the following formula (I):



(I)

wherein R^1 is C_1 - C_4 alkyl;
R^2 is tetrahydrofuranyl, C_1 - C_7 alkyl, C_1 - C_7 haloalkyl, C_2 -C_7 alkenyl, bicyclo [2.2.1] hept-2-yl or C_3 - C_8 cycloalkyl;
A is



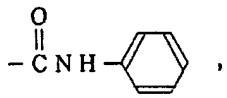
wherein R^4 is C_1 - C_4 alkyl;

Y is -O-, -S-, -O-N=CH-, -NR^5

-wherein R^5 is hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkylcarbonyl or pyridylmethyl, or single bond;

R^3 is C_1 - C_7 alkyl which is unsubstituted or substituted by one or more substituents, or -$(CH_2)_n$-B wherein n is an integer of 0 to 4, B is phenyl which is unsubstituted orsubstituted by one or more substituents, naphtyl which is unsubstituted or substituted by one or more substients, or heterocyclic residue which is unsubstituted or substituted by one or more substituents;

with the proviso that when -A-Y-R^3 is



R^1 and R^2 is not methyl at one time;

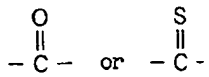
optical isomers, salts, N-oxide derivatives, hydrates or solvates thereof.

2. A compound as claimed in claim 1 wherein R^1 is methyl, R^2 is cyclopentyl.

3. A compound as claimed in claim 1 or 2 wherein R^3 is -$(CH_2)_n$-Bwherein n is integer of 0 to 2, B is heterocyclic residue which is unsubstituted or substituted by one or more substituents.

4. A compound as claimed in claim 1 or 2 wherein R^3 is -$(CH_2)_n$-Bwherein n is 1 or 2, B is heterocyclic residue having a ring of 6 atoms including 1 or 2 nitrogen atoms.

5. A compound as claimed in claim 1, 2, 3 or 4 wherein A is



Y is -O-, -S-, -NR^5- wherein R^5 is hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkylcarbonyl or pyridylmethyl, or single bond.

6. A compound as claimed in claim 1, 2, 3 or 4 wherein A is

Y is -O- or -NR^5- wherein R^5 is hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkylca rbonyl or pyridylmethyl.

7. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 6 and a pharmaceutically acceptable carrier therefor.

8. The use of a compound as claimed in any one of claims 1 to 6 in the manufacture of a medicament as a antiasthmatic.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 10 3196

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	CAS-REGISTRY HANDBOOK 1977 SUPPL. (STN DATABASE) * RN: 63140-31-8 *	1	C07D207/08 C07D401/06 C07D401/12 C07D405/12
A	CH-A-550 787 (A.H. ROBINS COMPANY, INC.) * claim 1 *	1,7	C07D403/06 C07D401/14 C07D403/12
A D	EP-A-0 511 865 (AMERICAN HOME PRODUCTS CORPORATION) * claims 1,7 * & JP-A-5 117 239 (AMERICAN HOME PRODUCTS CORPORATION)	1,7	C07D471/04 C07D409/12 A61K31/40
A	WO-A-91 16303 (ORION-YHTYMÄ OY) * example 12 *	1,7	
A,D	WO-A-92 19594 (SMITH-KLINE BEECHAM CORPORATION) * claims 1,8 *	1,7	
A,D	WO-A-91 15451 (SMITH-KLINE BEECHAM PHARMA GMBH) * examples 8,12,13 *	1,7	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D A61K
A D	FR-A-2 264 531 (SCHERING A.G.) * example 5 * & JP-A-50 157 360 (SCHERING A.G.)	1,7	C07C

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	30 June 1995	Frelon, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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